Medical Research Council of Canada
Conseil de recherches médicales du Canada

MEDICAL RESEARCH COUNCIL OF CANADA

GUIDELINES FOR RESEARCH ON SOMATIC CELL GENE THERAPY IN HUMANS

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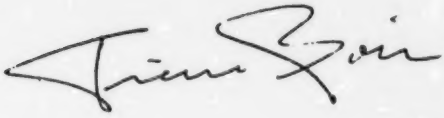
FOREWORD

The Medical Research Council has adopted these *Guidelines for Research on Somatic Cell Gene Therapy in Humans* as defining its requirements for all research which it funds in this area.

The Working Group, chaired by Dr. Patricia Baird, developed its report in the context of MRC's *Guidelines on Research Involving Human Subjects* (published in 1987) which apply to all research with human subjects.

A discussion paper was distributed to many in the scientific and academic communities and other interested persons, and written comments sought. The points raised were considered by the MRC's Standing Committee on Ethics in Experimentation and by Council in preparing these Guidelines.

The Medical Research Council thanks the members of the Working Group and all who participated in preparation of these Guidelines, and especially expresses its deepest appreciation to Dr. Patricia Baird.



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INTRODUCTION

There are over 4,000 different genetic diseases. While some of these diseases can be treated, and some are not severe, there remains a group of individuals who suffer greatly from devastating but presently untreatable genetic diseases.

While many of these genetic diseases are very rare and probably unfamiliar to most people, some are more common. For example, sickle cell anemia occurs with a frequency of 1 in 100 in certain African populations, 1 in 2,500 in American Blacks, and 1 in 6,000 among Europeans. Sickle cell disease can lead not only to severe types of anemia, but to multiple infections, and gangrene and tissue death from blockage of blood vessels. Blood transfusions are helpful in treatment, but victims are likely to live into adulthood only if they have close medical surveillance and repeated periods of intensive care in hospital. Other examples of genetic diseases that may be familiar to many readers are cystic fibrosis and muscular dystrophy.

While less common, Lesch-Nyhan disease occurs with a frequency of 1 in 15,000–20,000 births. It results in severe neurological signs including spasticity, mental retardation, aggressive behavior, and self-mutilation. It also results in kidney failure. Present treatment can ameliorate the kidney problem but does not remedy to any extent the nervous system problems.

As an example of a devastating disease affecting a particular population group, Tay-Sachs disease affects 1 in 3,600 infants born to Ashkenazi Jewish parents. The signs appear in the first year of life and cause nervous system degeneration with blindness, severe mental retardation, seizures and paralysis. Death usually occurs by the age of 5 years.

Recent advances in genetics and molecular biology offer the hope of treating some of these severe genetic diseases. Often referred to as somatic* cell gene therapy, this approach involves insertion of new genetic material into an affected individual's body cells to perform the functions that their faulty inherited gene is unable to carry out. Until the technique's safety and efficacy have been validated, it is premature to term the

* Somatic cells — body cells of an individual excluding cells in the sex organs that give rise to eggs or sperm.

technique "therapy". Although this term is often used for brevity's sake, in this document research in gene therapy should be taken to mean research interventions attempting somatic cell gene transfer.

It should be noted that laboratories in North America are now, or will be very soon, ready for the initial application of these technologies in patients.

The application of these new techniques raises a number of questions. Which diseases might be treated by these methods? What are the risks of these new approaches to the patients and their offspring, for others with whom they come in contact, and for society as a whole? How should we deal with the difficult ethical issues raised by clinical research into this new area?

The purpose of this document is to explore these questions by:

— outlining the medical and scientific background of research in this area;

— describing the potential risks and benefits to patients, their relatives, and society as a whole;

— defining the ethical concerns that must be addressed before research in somatic cell gene therapy is undertaken in patients;

— proposing regulatory processes to ensure responsible and thoughtful decisions in this area.

It is our view that, for the foreseeable future, somatic cell gene transfer should only be considered for diseases which meet all the following criteria:

— they are caused by a defect in a single gene;

— they cause a liveborn human being to suffer severe debilitation or early death;

— they cannot be treated successfully by any other means.

In our view there is no present indication for gene transfer research which deliberately alters the individual's germ line, and makes possible the passage of the inserted genes to future generations. Attempts to use gene transfer to enhance functions in people who do not suffer from severe debilitating genetic diseases are also not indicated.

1. MEDICAL AND SCIENTIFIC BACKGROUND

1.1 Background Genetic Information

Genetics is a young discipline which is rapidly evolving. Although some human diseases have been known to cluster in families for centuries, it was not until 1865 that Mendel discovered the principles of heredity and these did not receive wide recognition until the early years of this century. In 1953 Watson and Crick elucidated the structure of the molecule bearing genetic information — desoxyribonucleic acid (DNA), and it is only in the last decade that the fields of molecular genetics or "recombinant DNA" have evolved, with the ability to cut DNA into segments and then recombine DNA sequences from different organisms and transfer them to living cells.

All human beings inherit from their parents genetic information that defines such visible characteristics as that they are male or female, and the colour of their skin, eyes, or hair. These genes also carry instructions for many complex and detailed functions which enable individuals to move, speak, think, use foodstuffs and oxygen to provide energy, feel and respond to pain, or fight off infections through the immune system. Many factors in the physical and social environment modify and influence how the basic genetic makeup of the individual is expressed so that the overall characteristics of an individual are normally the result of a complex interaction between their genetic makeup and the experiences to which they have been exposed.

In some rare individuals the genetic makeup is such that it will not allow normal function in the usual range of human environments. It is for some of these individuals that research on somatic cell gene therapy may be of advantage. One example of a severe genetic disease would be Lesch-Nyhan Syndrome mentioned earlier. Another involves infants with adenosine deaminase deficiency (ADA deficiency) a condition that gravely impairs the ability to respond to infection so that death by two years of age is common after multiple episodes of severe infection.

Genetic information is contained in desoxyribonucleic acid (DNA) in a manner analogous to the way in which a written text contains information — a small number of letters arranged in a linear sequence. In a written text, 40 letters (if we include numerals, spaces and punctuations) convey information because they are arranged one after another to form words, sentences, chapters and volumes. In DNA, 4 chemicals are arranged one

after another to form codons,* genes, and gene control sequences. Genes are the functional units of DNA. They work by giving information for production of proteins in the same way as a recipe in a cookbook provides the information for production of a particular dish. Each gene codes for a specific protein such as globin, the protein part of hemoglobin which carries oxygen in red blood cells, or any one of the many enzymes that catalyse the chemical reactions that support life. Genes also contain controlling sections; these are directed by other genes, and regulate whether the gene is to be turned on or off, and the rate at which the gene makes its product (is expressed). For example, although all cells have the genes to make hemoglobin, most cells do not make it. It has been estimated that we have approximately 100,000 genes that code for proteins.

It is noteworthy that the DNA language is the same for all living species, though the "dialects" may vary; hence a gene derived from a lower animal may well make a protein with exactly the same function as that made by a human gene. Some important genes are highly conserved through evolution so humans share many genetic sequences in common with other species.

The information in a genome is read in much the same way as a computer would read an encyclopedia, or a cook would read a cookbook — a signal is the guide to the correct entry. This signal is a short sequence of DNA, or the name of the dish in the cookbook. If there is an error in either the signal or the name of the recipe stored, such that they do not exactly match, the stored information cannot be found and the information might just as well not be present. Further, mistakes in the entry itself can have varying effects on the information transferred. One wrong letter or word can totally change the meaning or spoil the dish, whereas another change might be much less important. The same is true for DNA. Some of these letters in the genetic code are in such important positions that, if even one is changed, the gene involved cannot function properly. If this gene is one of the many which are essential to early development, the embryo or fetus will either die in utero and be reabsorbed or spontaneously aborted, or be delivered as an irrevocably damaged infant. If the gene becomes important only in early childhood, an apparently normal infant will stop developing, become very ill and die. Some examples have already been described. An alteration in another gene might cause signs only

* A codon consists of three consecutive nucleotides in the DNA sequence and specifies an amino acid in the protein for which the gene codes.

in later life. Huntington disease is a particularly tragic example; it causes a progressive deterioration of the brain, usually starting in adulthood or middle age, and usually leading to death in 10–20 years. Other genes may affect the response to an outside environmental influence — for example, a chemical or a viral infection.

The genetic information for each human being is carried in 23 pairs of chromosomes. Each of the 46 chromosomes (23 pairs) is essentially a long strand of DNA containing genes coding for specific functions. We inherit one copy of each of the 23 different chromosomes from each parent, so that in general we have two copies of every gene. Thus each specific function in an individual is usually coded for by two genes — one from the mother, one from the father. All this information is contained in each nucleus of the many trillions of cells that make up the adult human body. While the hundreds of different cell types in the body all contain the same genes, they differ in which ones are "turned on" and being used to make protein. Some genes are expressed in all cells, whereas others are required only in one or two types of cells.

Of the 23 pairs of chromosomes, one pair determines the sex of the individual; males have an X and a Y chromosome, and females have two X chromosomes. In each of the remaining 22 pairs, the two paired chromosomes each code for the same functions, though the detail in the sequences may differ.

Except those on the X and Y chromosomes in males, for all genes there are two copies of each gene in each cell of an individual. If both copies in a gene pair code for fully functional gene products (which is possible even if they have slightly different sequences), the individual will be normal. If both copies code for defective products which normally are essential for life, the individual will have a lethal disease. If one member of the pair is normal, and the other defective, the fate of the individual will depend on whether there is sufficient normal product from the normal gene to allow healthy function.

1.2 Categories of Genetic Disease

Diseases that are determined by genetic differences can be divided into three categories — single gene disorders, chromosomal disorders, and multifactorial disorders. It is important to clarify the distinction between "genetic" disease and "congenital" disease. "Congenital" simply means "present at birth" and has no implication with regard to cause. Some congenital conditions are genetically determined, some are not. Conversely some genetic conditions are evident from birth, some are not.

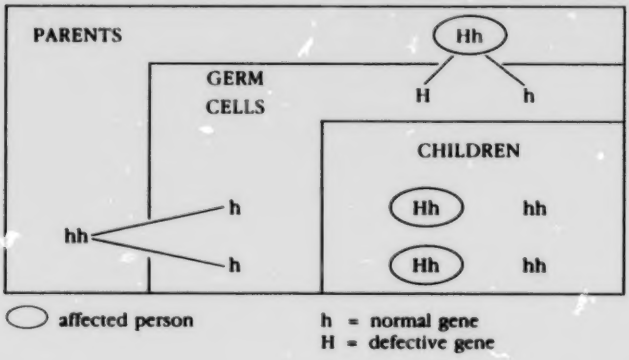
1.2.1 Single Gene Disorders

Disorders determined by single genes are caused by a defect in a single pair of genes. They may be transmitted in a dominant, a recessive, or an X-linked way.

In dominantly inherited disorders, only one member of the gene pair needs to be abnormal to cause the disease; the normal member of the pair is unable to cover for its malfunctioning partner. If the affected person reproduces, the abnormal gene will be passed on average to half their children who will also be affected (Fig. 1). Huntington disease is an example of a dominantly inherited single gene defect.

Figure 1

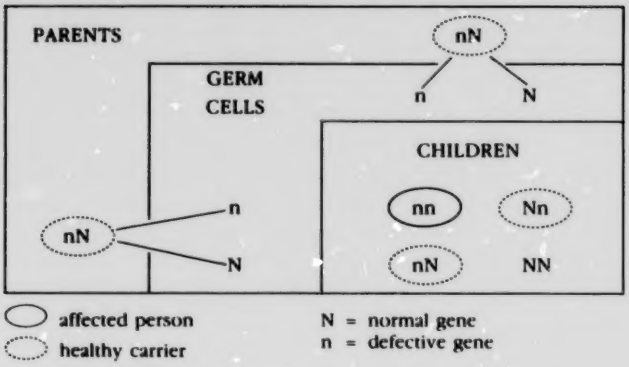
TRANSMISSION OF DOMINANT DISORDERS



For recessive disease to occur, both genes in the gene pair — one received from the mother and one from the father — must be abnormal. In this category, one normal copy of a gene is able to provide enough product to cover for its malfunctioning partner. If the parents each have only one abnormal member in the pair, they themselves are unaffected. However, as shown in Fig. 2, when both parents carry the defective gene, on average one quarter of their offspring will have both genes faulty and thus be affected. Examples of recessive disorders are phenylketonuria (which results in retardation and seizures but can be treated by diet) and adenosine deaminase deficiency (which results in severe immune deficiency and early death). Another more widely known recessively inherited disease is cystic fibrosis, which is one of the commonest recessive disorders in Caucasian populations and leads to severe chronic respiratory and digestive problems and a reduced life expectancy for most affected individuals.

Figure 2

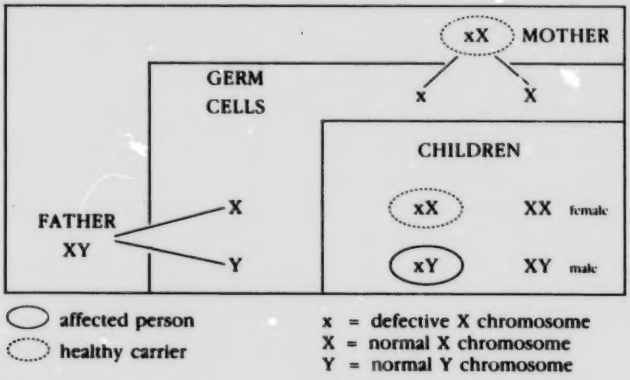
TRANSMISSION OF RECESSIVE DISORDERS



In X-linked recessive disorders, the problem gene is located on the X chromosome. Since females have two X's, if one is normal, that female will be healthy. Since males only have one X, if this has the X-linked disease gene, they will be affected. In these families therefore, as shown in Fig. 3, females may be healthy unaffected carriers of the gene, but half of their sons will have the disease. Some examples of X-linked single gene disorders are hemophilia (a bleeding disorder which can be partially controlled with injections of blood clotting factors), and Lesch-Nyhan Syndrome mentioned previously.

Figure 3

TRANSMISSION OF X-LINKED RECESSIVE DISORDERS



Each one of these genetic disorders is relatively rare. Even one of the commonest, cystic fibrosis, occurs only in 1 in 2,500 births, whereas others are much less frequent; most recessive

disorders have a birth incidence of 1 in 15,000–100,000. However, since there are so many (as noted before, over 4,000 known) single gene determined disorders, these have a considerable impact; current knowledge indicates that as many as 3% of all liveborn individuals will have a single gene determined disease.

1.2.2 Chromosomal Disorders

Genetic diseases in this category are due to extra or missing chromosomes or parts of chromosomes. For example, individuals with Down Syndrome (Trisomy 21) have three copies of chromosome 21 instead of two, and show developmental retardation and various physical abnormalities. The incidence at birth of various chromosome abnormalities is 1 in 200 liveborn individuals. These are not amenable to gene transfer with the present state of knowledge.

1.2.3 Multifactorial Disorders

Multifactorial disorders are the third category of genetic disorders. In this group, complex interactions between environmental factors and the genes of an individual cause disease in ways which we are only beginning to understand. Some examples are common congenital malformations such as neural tube defects (spina bifida and anencephaly), congenital dislocated hips, and some adult onset disorders such as atherosclerosis, hypertension, schizophrenia, and some cancers. It is likely that most familial chronic diseases of adult onset that have major impact on our health care and social systems fall into this group. These disorders are not accessible in the foreseeable future to gene transfer because of their complexity; many may respond to modification of the patient's lifestyle. This is by far the largest category of genetic disease; it appears that at least 1 in 10 individuals in the population are affected by multifactorial disorders.

1.3 Non Inherited "Genetic" Disorders

Some people who are normal at birth may acquire disease caused by modification of the DNA in a particular type of cell. Genes may be damaged or the genome in some cells altered by environmental agents such as radiation, chemicals or viruses. Examples of such diseases are cancer and acquired immunodeficiency syndrome (AIDS). Gene insertion technology is likely to have broad application in the treatment and monitoring of such human diseases. Future applications are expected in the field of bone marrow transplantation (e.g., tagging of transplanted cells with gene markers to monitor them, modification of chemotherapy resistance or immunogenicity) and in the treatment of diseases due to persistent viral infection, such as AIDS.

1.4 Other Human Characteristics

Many human characteristics such as intelligence, appearance, kindness, etc. are determined by the interactions of the effects of a number of genes with the environment. The possibilities of being able to modify characteristics such as these by changing the DNA of an individual are now so remote as not to merit anything more than distant speculation. The difficulties to be overcome even to correct the DNA of an individual with a well studied single gene determined disorder are formidable. We are much more likely to be able to influence desirable complex characteristics by lifestyle changes or controlling our environment than by genetic manipulation for the foreseeable future. To attempt genetic interference in such characteristics would be not only unjustified but repugnant to most Canadians.

1.5 Research in Somatic Cell Gene Therapy

It is now possible to isolate particular genes, together with additional DNA containing necessary regulatory sequences. It is very probable that the technology will soon be available to insert such genetic material into cells taken from a patient suffering from an inherited disease and return the altered cells to the patient in the hopes of correcting the disease. In such research protocols, the steps in transferring a gene to a patient might involve the following:

— Precise genetic diagnosis including demonstration of a mutation in the relevant gene of the individual.

— Obtaining copies of the relevant normal gene from human DNA (or from non-human sources if there are reasons to expect that this is likely to be more effective.)

— Removing appropriate cells from the patient.

— Inserting copies of the normal gene into an appropriate number of patient cells. Since a clinical effect can be expected only if sufficient numbers of patient cells have the new gene, methods to help the treated cells to survive and grow in the patient may be required.

— Ensuring that the newly inserted DNA is expressed properly in the patient's cells.

— Transplanting the modified cells back into the patient.

— Closely observing the patient to determine success or failure.

DNA may be introduced into human cells by one of several methods. The cell membrane of the host cells can be made more permeable by treatment with calcium phosphate, or by small electric charges so that DNA can enter. It is also possible to insert DNA segments physically (e.g. by microinjection). At this time the most efficient method of delivering genes is to incorporate them into a special group of viruses, called retroviruses.

Retroviruses are effective agents for gene transfer because they can infect cells with a very high efficiency, and integration of their genetic material into the host cell's chromosomes is one step in their life cycle. It is essential that the retroviruses used to carry in the DNA of interest be disabled so that they do not remain infectious once incorporated into a cell. These disabled viruses used to carry in new genetic sequence are called viral vectors. Retroviruses have been associated with the formation of cancers so, again, it is important the they be disabled.

Practical difficulties at present limit the range of genetic diseases that might be treated by this approach. Even though the rapid growth of molecular biology makes it likely that many genes will soon be identified and obtained in a pure form, these practical difficulties mean that few inherited diseases are likely to be suitable candidates for research in gene therapy. Examples of some practical difficulties are:

1. The clinical consequences of the disorder must be due either to effects occurring in a single accessible tissue (e.g. blood, bone marrow, liver), or to changes in a protein or metabolite (e.g. growth hormone, phenylalanine) that circulates freely in the blood in amounts which could be affected by the action of a gene inserted into a particular accessible tissue.

2. In gene disorders that affect relatively inaccessible tissues such as brain or bone, it is difficult to envisage how it might be possible to correct the disease that has occurred in a fully formed human individual, for example, by reversing the marked shortening of the bones seen in a severe skeletal dwarfing condition once the skeleton is formed. Similarly, if a gene disorder affects many tissues, or produces irreversible malformation or damage from toxic metabolites, it is hard to see how replacement of the defective gene could be effective.

3. For normal function, a gene must not only be present, but it must be expressed at the normal time and in normal amounts. Although our understanding of gene regulation is in its infancy, very rapid advances are being made. One example where gene regulation will be important is in inherited blood diseases such as sickle cell anemia and the thalassemias of which there are several forms, some resulting in severe anemia and early death. These result from mutation in the globin genes. Until our understanding of globin gene regulation increases, these diseases may be poor candidates for research on gene therapy because of the need for precise regulation of expression of the gene. In contrast there are some diseases where the gene product is not very narrowly controlled, and circulates freely; these diseases may be more amenable to initial attempts at research on gene therapy. For example,

in adenosine deaminase deficiency (which causes early death due to problems of immunity) the product is not very narrowly controlled and it may therefore be more immediately accessible to treatment.

4. Genes must be inserted into enough cells so they produce enough product to have a significant effect on the course of the disease, but not so much that the inserted genes themselves cause new disease.

5. For the foreseeable future it is likely that only recessive disorders would be candidates. DNA cannot yet be reliably targetted to integrate at a specific site in the host genome and replace a dominantly acting mutation.

6. The inserted gene must be stable and continue to make the gene product over a long period of time.

7. There may not be an animal model for the human disease so that it is difficult to evaluate the potential outcome of transferring the particular gene.

Further, the answers to some troubling general biological questions raised by gene transfer are not known. For example, will the normal protein resulting from the inserted gene be recognized as foreign by the patient's immune system which then mounts a response leading to serious clinical consequences? A second concern is that, while several approaches to inserting foreign DNA have been used, there is not good control over the site of insertion. If genes are inserted randomly into a recipient cell's DNA, it is possible that this could cause mutation — for example, in important genes controlling growth and differentiation. The statistical likelihood of this is very small since the proportion of our DNA which is taken up by coding genes is probably less than 5%. However, if a normal gene is expressed inappropriately as a consequence of this insertion, the outcome for the patient is unknown and the possibility of a disease such as cancer is a concern. More specific methods for inserting genes into their correct sites in chromosomes may allow more precise gene manipulation and reduce this type of risk; this is a very active area of investigation.

1.6 The Effects of Somatic Cell Gene Transfer on the Human Gene Pool

One concern surrounding gene transfer is its potential impact on the human gene pool. In this regard, it is important to emphasize that, because somatic cell gene therapy will not alter the germline, its effect on the distribution of genes in the population will be no greater than has already resulted from the introduction of other successful therapies for inherited disease. The human gene pool is already being altered by current traditional methods of treatment for genetic disease (e.g. for phenylketonuria) which

allows affected individuals to grow up and have children. The net effect of somatic cell gene transfer, if successful, will be to allow a desperately sick individual to lead a normal life. If the treated individuals go on to have children, they will pass on the genes they received from their parents; they will not pass on the inserted genes, as only their body cells, not their germ cells, have been changed. In fact there are many analogies to organ transplantation or to introduction of treatments for hemophilia, juvenile onset diabetes or cystic fibrosis.

The frequency of a "harmful" gene in the population depends on its mutation rate (how fast it is formed), and how stringently the environment selects against it (how fast it is removed by not being passed on to children). At present, most diseases caused by mutant genes are rare because there has been strong selection against them over the millennia; affected individuals have not often reproduced. For the recessive genetic disorders with which we are concerned, the overwhelming proportion of relevant genes exists only in one dose in individuals — the carriers (heterozygotes) who are not sick. If, because of treatment, affected individuals are able to grow up and have children, the number of extra harmful genes added to the human gene pool is negligible. The reason for this is that these individuals are so rare, whereas the carriers having one dose of the gene are common. For a recessive disease with a present frequency of 1 in 10,000 births, 1 in 50 of the population are heterozygotes. It can be estimated that after 100 generations of fully normal reproduction by successfully treated homozygotes, the frequency of the disease would be 1 in 2,500 births, so that the rate of increase would be small. Successful treatment of X-linked diseases would increase the gene frequency at a somewhat greater rate than this.

1.7 The Effects of Gene Transfer Affecting Germ Cells

Because it may not be possible to correct damage due to a genetic disorder which has already occurred during embryonic development early in pregnancy, it may seem logical to attempt therapy before the damage has occurred. For many disorders, this may lead to a perceived need to insert the correct gene while the system it affects is developing, for example, during embryogenesis or fetal development. Since the advent of *in vitro* fertilization the most practical time to have access for manipulation is in the preimplantation stage of the embryo. If genes are inserted early enough in embryogenesis to become incorporated in that embryo's gonads, not only the individual but their offspring may be affected. This opens up a far wider range of ethical implications. In contrast to somatic cell gene transfer,

manipulation of the genome that individuals can pass on to their children raises unique ethical concerns and profound difficulties in the minds of many people.

The concept of gene transfer very early in embryogenesis is in fact not very relevant to therapy of human genetic defects. Genetic disorders can be diagnosed at this early preimplantation stage of embryogenesis if the early conceptus is *in vitro*. However, once diagnosed, an alternate choice is simply not to implant affected embryos. While this raises ethical difficulties for some individuals, this is probably a less hazardous course than to implant a defective embryo which, in addition, has been genetically manipulated. The instances where couples would not be able to have healthy children without genetic manipulation are theoretically very few — a vanishingly rare instance being where both parents suffer from a recessive disease because both carry the same recessive gene on both of their chromosomes. Even then it could be argued that if the disease is mild enough so that individuals consider having children, the disease is not severe enough to be a candidate for research on gene therapy. Gene manipulation at this early stage has therefore no justification at this time in humans.

Another concern raised regarding gene transfer which also affects the germ line is that there is a potential for changes in the human gene pool. Theoretically, the genes added to the gene pool, if this approach were successfully used, would code for normal products. If future changes in technology and knowledge raise consideration of gene therapy in humans that would affect the germ line of an individual, then risk and benefits would have to be very carefully weighed. At this time there is no indication for such proposals in humans.

2. ETHICAL ISSUES

2.1 Research or Therapy

A physician should only undertake therapy outside standard medical practice when the outlook for the patient otherwise is dismal, and when the scientific team and the physician are able to master all the aspects of the proposed therapy. Research on somatic cell gene therapy demands a team of highly specialized scientists, preferably including the patient's physician. Since many of the questions and concerns in this complex new area demand research, the Working Group believes that the use of gene transfer techniques in humans should be viewed as research at this time, and that any proposal to use gene transfer techniques in a human subject be considered for ethical acceptability as a research proposal before being implemented.

Change to the genome of treated individuals has implications that need to be carefully weighed and there is a clear need for the information obtained to be scientifically valid. It is therefore the view of the Committee that all gene transfer techniques used in human subjects fall within the context of clinical research, and thus require approval of the Research Ethics Board (REB) as defined in the *MRC Guidelines on Research Involving Human Subjects* (1987).

The Committee also hopes that provincial Colleges of Physicians and Surgeons and other local levels of medical authority will take the same view if approached by physicians who wish to treat desperately ill patients under the rubric of innovative therapy.

2.2 Consent to Research in Somatic Cell Gene Transfer

2.2.1 Background

While it is true that some genetic diseases do not express themselves to the same degree and at the same age in each individual, the diseases which meet the criteria for suitable candidates for research on somatic cell gene therapy afflict patients in very similar ways. The damage caused is often progressive, cumulative, and fatal at an early age. This leads to a dilemma. On the one hand it seems appropriate to treat individuals as soon as they have been diagnosed to maximize the potential for therapeutic benefit if gene transfer is successful; the risks of performing gene transfer will not be reduced by waiting, and delay will almost certainly cause greater harm to the patients through irreversible accumulation of the effects of the disease. On the other hand, the younger the subjects, the less able they are to consent. A basic principle of the ethics of research is that competent subjects

should be chosen if possible; however, patients with some candidate genetic diseases do not attain the age of consent, or even meaningful assent.

2.2.2 The Elements of Informed Consent

It is a fundamental principle that human beings can only be involved as research subjects if they have freely consented after fully understanding the research to be undertaken and their role in that research. This principle and the difficulties of implementing it when the patient is a child are fully described in the 1987 MRC Guidelines. Briefly, and at the very least, a potential research subject, or the person (proxy) who is to give consent on behalf of the subject, must understand:

(i) the reason(s) he or she has been selected to participate in the proposed study;

(ii) the nature and objectives(s) of the research;

(iii) the harms and benefits associated with participating or refusing to participate in the research;

(iv) the available alternatives and the harms and benefits associated with these;

(v) the probability that any of the potential harms or benefits will manifest themselves;

(vi) the qualifications/experience of the researcher(s) involved; and

(vii) that the consent to participate can be withdrawn at any time with no adverse effects to ongoing medical care.

2.2.3 Consent with Special Populations

a) Research involving children

The elements of informed consent by the subject outlined above may not be completely met in the case of research on gene therapy, for several reasons. First, the most suitable candidate diseases are usually lethal, or cause mental retardation, at an early age; proxy consent is therefore essential. Since clinical trials on severe early onset disease necessarily involve very young children, there is an ethical dilemma; restricting research on gene therapy to those subjects able to consent will exclude the most severely affected patients in whom there is early onset of the disease and rapid deterioration. These have been identified above as probably the most suitable candidates. The greatest potential benefit of research on gene therapy is before deterioration is irrevocable. However, these are the subjects least able to consent for themselves. The Working Group is very conscious of the problem this dilemma poses. Within the context of research, it is clear that

there is the potential of gaining the most knowledge in these diseases if trials are carried out on the earliest diagnosed patients even though these are just the individuals who are least able to give consent or even assent. The potential benefit to the individual child is also greatest before irreparable damage from the disease has occurred.

A unique aspect of research on human gene therapy concerns the option of withdrawing. The insertion of genetically modified cells cannot be undone; the gene transfer is irrevocable, so for some aspects a consent cannot be withdrawn. Further, long term monitoring is important to assess potential harm to the patient or to third parties. By withdrawing, the patient will not only lose the benefit from early recognition of harms to himself which might only manifest themselves later on, but will also deny any future subjects the benefits of the information to be derived from long term monitoring for harmful effects, and will make it difficult to assess the hazards to the community.

While the rights of the individual prohibit enforced compliance, it seems appropriate that, at the least, the prospective research subject, or the person giving a proxy consent, understand the potential long-term risks prior to consenting to increase compliance after the initial intervention. Proxies must understand that they may not have the right to withdraw a child from those portions of a protocol to which they have committed the child and which are therapeutically indicated. The situation could then be subject to the common law duties of a parent to provide medical necessities to the child. If remaining in the trial is in an incompetent subject's best interest, then this might be upheld in court. Since there are possible harms to others, it is appropriate to persuade the subjects to continue in long term follow-up. In the absence of settled law on this point, what would happen if a person nevertheless withdraws is open to question. In cases where there is possible harm to others, public policy might well overcome the individual's right to withdraw.

Full disclosure of risks is required for the subject to provide a valid informed consent to research. The risk of a harm should not only be quantified as accurately as possible but the harm itself described; the patient's or proxy's perceptions of potential harms may differ markedly from those of the physician, and a high risk of trivial harm may be acceptable, whereas a low risk of a very serious harm may not.

As children cannot provide a legally or ethically valid consent to research, consent must be sought from the parents or guardians. The decision by a parent or guardian to permit a child to participate in research on somatic cell gene therapy must be

based on the same information which would be given to competent prospective research subjects. Because the proposed genetic intervention may be the child's last hope, parents and guardians may be willing to ignore the risks and to focus instead on the possible good; they may therefore be too eager to consent to their child's participation in the research. Their hope must be tempered by an adequate understanding of the risks involved. Feelings of guilt about transmitting a genetic disease may influence some parents to downgrade the risks of gene transfer. On the other hand some parents may inadvertently become over-protective and thus over-rate the risks. Provision should therefore be made in the protocol to ensure the availability of in depth counselling to ensure full understanding by the subject or legal guardian of what is proposed in the protocol.

Though parental consent is necessary for research on children, it is not binding. A child may express a desire not to participate and this expressed wish should be respected. The MRC *Guidelines on Research Involving Human Subjects* stipulate that "parental consent may be a necessary condition of engaging the child in research, but it is not necessarily a sufficient condition; the child's negative preferences in such cases should be respected" (p. 29). Given this, children should be encouraged to participate in the consent process to the extent to which they are capable. Unfortunately, this proviso may not be relevant to the children suffering from diseases suitable for research. For example, research with possible therapeutic benefit for ADA deficiency must be started with infants or young children; the severe mental retardation often present in those patients with recessive diseases who will be candidates for gene transfer may make it impossible for the child to register either assent or dissent. In addition, some provinces have particular rules with regard to the consent process regarding adolescents and minors.

b) Research involving human fetuses

In the future, if somatic cell gene therapy is shown to be effective and safe, it may become an appropriate strategy for diseases which result in irreversible damage by the time of birth. In this situation, the proposed genetic intervention would have to take place early enough to benefit the patient, but late enough to ensure that the germ cells would not be affected (i.e. the gonads had already fully formed.)

In the view of this Working Group, research in somatic cell gene therapy for the conceptus *in utero* should not be done at this time; it would be irresponsible to incur the added risks to the mother involved in prenatal therapy without convincing

evidence that somatic cell gene transfer can be effective in individuals after birth.

2.3 Evaluation of Risk and Benefit

The 1987 *MRC Guidelines on Research Involving Human Subjects* clearly stipulate that the foreseen benefits must outweigh the foreseen risks in order for any research proposal to be approved. Accordingly, the probable safety and effectiveness of a proposed research project will have to be carefully evaluated with particular attention given to the potential risks for both the individual and society at large before approval is given. This is a difficult area in which to make judgments, as not only do risks and benefits to an individual and to society have to be weighed, but the balances of benefits to society and risks to individuals, and vice versa, need consideration.

2.3.1 Risks for the Individual

Gene transfer using somatic cells, in humans, though potentially beneficial, has important potential risks:

— Viral vectors used to deliver the gene of interest to the host cells may recombine with undetected viruses and regain their infectious properties or perhaps affect endogenous DNA sequences and produce malignancy. Thus, information addressing these risks is needed. The risk of malignancy as a result of treatment is not confined to this new approach; it also is a consideration in radiation therapy for cancer, immunosuppressive therapy used in transplantation, and the use of drugs with the risk of causing cancer, such as the antibiotic chloramphenicol.

— There is the possibility that a functioning host gene may be interrupted by the random integration of a foreign DNA sequence, and thus have negative consequences for the patient.

— The presence of bacterial contaminants in the DNA inserted into the patient's cells could cause unwanted side effects.

— The use of strategies designed to help the engineered cells establish themselves in the patient may have hazards which will need to be considered in the assessment of risks.

— There is a possibility that the inserted gene might inadvertently become transferred to their germ cells and might affect their offspring in an unanticipated way.

— If insufficient gene product is produced by the genetically modified cells, the genetic disorder may be only partially corrected so that the lethal genetic disease could be converted to one where the individual survives but suffers greatly.

2.3.2 Risks for Society

The risk of viral vectors again becoming infectious during somatic cell gene transfer must also be considered from a community perspective. These viruses might then be transmitted inadvertently to persons with whom the patient is in contact, for example, relatives, friends or health care personnel.

The possible impact on the composition of the human gene pool must also be considered. If individuals with rare lethal genetic disorders are successfully treated by means of somatic cell gene transfer, they may choose to reproduce. As discussed in the previous chapter, this would increase the number of abnormal genes in the gene pool since they may pass on the abnormal genes to their progeny. However, as noted, since human gene transfer is likely to focus on recessive disorders, the population impact would be extremely small. It could also be argued that any medical treatment of genetic disorders, including prenatal diagnosis, has some impact on the human gene pool. In fact, somatic cell transfer could be expected to have less of an impact on the gene pool than many other medical interventions.

The most serious risk for society concerns the possibility that the new genetic information will inadvertently be transferred from somatic to germ cells, and thus to the next generation. In the short term this could mean that an individual's offspring would be adversely affected by some unintended mutation. In the long term, the consequences are unknown. The impact is likely to be very small since only children of the small number of treated individuals could contribute to the gene pool. The human gene pool could be altered but the increase judged in the context of the total numbers of mutations that are constantly occurring would be infinitesimal. It is not appropriate to approve any protocol where the germ line is foreseen to be altered, even though this is not the primary intention of transfer.

2.3.3 Minimization of Risk — Maximization of Benefit

a) Safety and efficacy

Before a proposed trial for somatic cell gene transfer involving humans is approved, the likelihood of benefit to the research subject must be well documented. This means that both the safety and the efficacy of the proposed genetic intervention must have been carefully assessed. The proposal should show that cells with the transferred gene have been obtained and are capable of producing an active gene product. Data with regard to efficiency and appropriate expression in target cells *in vitro* and *in vivo* are needed. Whenever possible, a human gene should be used. However, in some circumstances it may be acceptable to propose a non-human DNA sequence for transfer. As noted under

3.3.2, if this is the case, then the reasons why a human gene is not appropriate should be clearly documented. In this case it is important to remember that the objective is therapy to return toward normal function.

Both technical and animal data must be provided showing that every possible precaution has been taken to assess and to minimize the risks. For example, to reduce the risk of infection and/or malignancy, all vectors used must have been shown to have been disabled so that they cannot replicate themselves. Information regarding the risk of unintended transfer of the vector to the germ line must be available.

b) Animal models

Ideally, the safety of any proposed research protocol involving humans should be assessed on the basis of animal trials designed to study both the short term and long term impact. One important study will be to assess the risk of infection and malignancy by assessing whether the foreign DNA remains and functions in the host cells without harming them or other cells; another will be to observe treated laboratory animals throughout their life span to address the risk of cancer; it will also be important to study the offspring of these research animals to determine possible effects on subsequent generations and if there has been any transfer to germ cells. However, safety demonstrated in studies on animals does not guarantee lack of harm when used in humans. Ideally these trials should be conducted not only on mice and other small animals but also on primates, from which the findings may be more relevant when extrapolated to humans. There should be demonstration of correction of the disease if appropriate animal models exist.

There are no known animal models for the enzyme deficiency diseases which are likely to be early candidates for trials of somatic cell gene transfer in humans. For example, mice carrying the gene defect responsible for Lesch-Nyhan syndrome seem to function quite normally. Consequently, the potential for success may have to be assessed as far as possible on the basis of tissue cultures and research with animals. For other genetic disorders, however, it may be possible to assess efficacy on the basis of animal trials. As a minimum requirement prior to clinical studies, research with animals would have to show that:

1) new curative genes can be directed to specific cells and remain there long enough to be effective;

2) the inserted genes can express their product in the target cells at an appropriate level; and

3) no harm results to the treated cells, to the test animal or to its offspring.

Researchers should therefore provide the Research Ethics Board (REB) with detailed information about the precautions taken to minimize the various risks, and provide animal and cellular data relevant to whether the proposed research would benefit the patient.

c) Selection of candidate genetic diseases

Obviously, research involving human subjects should only be undertaken if the anticipated benefits are expected to outweigh the possible harms. This means that initial trials for somatic cell gene transfer should only be considered for persons afflicted with serious genetic disorders (i.e. severely debilitating and/or rapidly lethal diseases) for whom there is no effective conventional treatment. Only if the burden imposed by the inherited disease on the afflicted individual is great and no satisfactory therapy is available, or the available therapy entails greater risks and less benefits, might clinical trials for somatic cell gene transfer be justified. There should be demonstration of accessible and appropriate target cells and of the possibility of amelioration if a functioning gene could be inserted into these cells. If the clinical trials for devastating diseases prove to be effective and safe, then research on somatic cell gene therapy might be considered in the future for less burdensome diseases such as haemophilia or PKU for which there are alternative treatments. It is clear that in the foreseeable future, research on somatic cell gene therapy should be limited to serious and untreatable genetic disorders for which there is no effective alternative treatment.

d) Selection of research subjects

The selection of research subjects must take into consideration the numbers of individuals to be treated in the first trials, and whether treatment should be restricted initially to one candidate disease. Experience has shown that it is very rarely possible to predict the success or failure of a new therapy on the basis of one or two cases. Beneficial approaches might not succeed in the first few subjects, or might even show harm; conversely an actually unacceptable method may be highly successful in its first few attempts. The arguments are essentially statistical; throwing heads three times in a row does not allow the prediction that the next 97 times will also be heads. For such reasons, a decision to start research on gene transfer in patients must recognize the intent in principle to treat a number of individuals, even though there can be no doubt that each patient must be studied very carefully to discover unexpected outcomes or to apply what can be learned from this experience to the next patient.

It has also been suggested that studies should be undertaken initially only on treatment for one genetic disease meeting the criteria outlined above. The Working Group rejects this view with one opinion to the contrary. Most committee members felt that, because these diseases are different, the genes added to human somatic cells to treat different diseases cannot be expected to behave in similar ways. However, experience with one means of therapy may provide useful information about risks associated, for example, with the method of inserting the new gene into the cells, and this information should be taken into consideration in later decisions.

One member believes it is contradictory to say that important information about risks of gene insertion can be learned from an experiment about one disease and applied to other diseases, while saying that each study protocol should be treated independently of protocols on other diseases. In that member's view, ethical requirements that the risks of research be minimized and scientific value and validity be maximized require that, in the initial stages of somatic cell genetic manipulation in humans, the early results of each approved protocol be reviewed and analyzed by an independent team before any further protocols are approved.

Since the genetic diseases for which research on somatic cell gene therapy may be suggested are rare (1/15,000–1/100,000) it is possible that research groups may be in competition to attract prospective subjects to their particular research centre. Alternatively, since centres trying the new methods are also likely to be few, it is possible that there will be more affected individuals than can properly be incorporated into trials of a new therapy. Hence, equitable criteria for selecting research subjects are important.

In summary, the selecting criteria should be clearly documented and submitted to the REB for approval.

e) Selection of genetic sequence

The Working Group is of the opinion that the DNA sequence to be transferred should preferably be of human origin. The ethical concern regarding a non-human sequence arises with respect to those sequences designed to be integrated as a functional portion of the subject's genome, the so-called 'target gene', or 'gene of interest', as opposed to those sequences, commonly derived from viruses, employed as a delivery system into the genome. The use of permanently functioning non-human genetic sequence in somatic cell manipulation differs from other therapeutic uses of non-human materials, (e.g. animal-derived insulin) in its

irreversible alteration of the subject at the most fundamental genetic level. Most important, while the restriction of gene alteration to normal human sequences would confine such manipulation to therapeutic use, allowing the insertion of a non-human sequence would blur the crucial ethical distinction between therapy and enhancement. Therefore, the review body should apply an enhanced requirement of scientific justification to protocols intending the insertion of a non-human genetic sequence as the functional target gene. However, circumstances can be envisaged under which it may be appropriate to approve research protocols in which the gene to be transferred is from a non-human source. It might be desirable, for example, to use additional bacterial DNA sequences that would convey resistance to certain drugs and hence facilitate selection of cells in which gene transfer has occurred. Also expression of transferred genes might require, or be better controlled by, use of non-human regulatory sequences. If a non-human sequence is to be used, the reasons why this is proposed and why human sequence is not as likely to be of benefit must be fully documented, and the above concerns taken into consideration.

f) Long term monitoring

With this research, there is a potential for harm to third parties, to the subjects themselves after many years (e.g. late development of cancer), and to the offspring of the subject. The proposal should address the issue of long term monitoring of the research subjects and the outcome of their reproduction. Details on how long monitoring will be carried out, how adverse outcome will be evaluated and what strategies will be followed to handle it should be given.

2.4 Confidentiality

A further principle which must be recognized is the subject's right to control personal information. Information obtained during research on somatic cell gene therapy may be prejudicial to the patient or family. Any information obtained on subjects must be reported in a manner which conceals their identity. Identifying information can only be disclosed with the subject's or proxy's expressed authorization. This is especially important since the first clinical trials of somatic cell gene therapy are likely to be of great interest to the media and the public at large. Since the initial trials will involve children, the parents or guardians — not the researchers — must decide whether it is in the child's best interest to be publicly identified, and whether any personal/confidential research data are to be disclosed.

3. ETHICAL AND SCIENTIFIC REVIEW

The MRC's requirements for ethics review are fully described in its *Guidelines for Research Involving Human Subjects*, published in 1987. In this chapter, we consider only issues of special relevance to human somatic cell gene transfer.

3.1 Guidelines compared to Legislation

The *MRC Guidelines on Research Involving Human Subjects* consider whether legislation or guidelines are more appropriate to regulate research on human subjects, and conclude that Guidelines are preferable at this time. Guidelines are more flexible and "can accommodate more easily than law the shifting social evaluations that affect research, and can influence responses in subtle ways rather than with the rigidity often found in legislation" (p. 11). The law is a blunt instrument, and cannot effectively address the relevant complex ethical issues. This is especially true for research in human genetics, which is rapidly evolving and constantly raising new issues. It is even more the case for research in gene transfer where knowledge is changing very quickly.

The second reason for preferring guidelines concerns the constitutional distribution of power between the federal and provincial governments; health, hospitals, universities, majority age, and mental competency are under provincial jurisdiction. Thus, proposed legislation could differ from province to province. The third reason for preferring guidelines to legislation is closely tied to the overarching objective of encouraging ethical responsibility. Guidelines promote thoughtful decision-making among researchers and members of REB's. An awareness and understanding of ethical values is achieved not by blind adherence to law, but rather by a careful consideration of the options and an exercise of reasoned choice.

3.2 The Review Process

The MRC Guidelines require research involving human subjects to be reviewed and approved by local REB's before it is undertaken. Local review is preferred as the usual process because it allows for local resolution and awareness of ethical issues; because the needs and interests of different communities may differ across the country; and because it may be more effective than a national review carried out, of necessity, at a distance.

On the other hand, review of proposals in somatic cell gene transfer in human subjects is extremely specialized, is of

great public interest, and raises a number of new issues. Therefore review at a national level in this area might have several advantages. There would be greater access to experts in such specialized areas as retroviruses, infectious diseases, pediatrics, and human genetics. A local institution may not have sufficient members with the background and knowledge to review a protocol for somatic cell gene therapy because the needed local experts are likely to be involved with the proposed research. Any one centre is unlikely to have enough experts who are completely at arm's length from the proposal to decide objectively some of the more complex issues.

Another factor in favor of a national review is the need for uniformity in the application of the proposed guidelines. A national committee would allow knowledge of progress in the field to be shared more readily. Such a committee could also have a monitoring function which would allow information to be rapidly communicated, and deal with the issue of overlapping or duplicate proposals. There may be a need to ensure that the minimum number of individuals are exposed to the potential harms while ensuring that the essential clinical and research questions can still be answered. Given public concern about human gene manipulation and the ability of scientists to deal impartially with the complex ethical implications, it may be helpful to have a national overview, if only to provide checks and balances. Canadians may prefer to know that one body is overseeing this area of research. Although the principle of local responsibility is important and it is possible for a local committee to import needed expert advice, it is difficult for invited expert opinion to override a local committee.

After consideration of all these points, the Working Group unanimously and strongly recommends a two-tier process be put in place. This would involve a review by the local REB; if positive, the proposal would be forwarded to a National Review Committee before implementation.

As well as reviewing proposals for approval or rejection, a national committee should also collect ongoing information on research results and monitor national experience for adverse outcomes.

It is expected that the need for a National Review Committee will diminish over the years as experience is obtained in Canada and in other countries. It is therefore recommended that this committee have a finite lifespan and that the need for it be evaluated at the end of that time.

It is recommended that all proposals funded by MRC utilizing gene transfer in humans be required to come to this National Review Committee. It is the view of the Working Group

that other responsible agencies, such as hospitals, pharmaceutical companies and research granting agencies, should also consider referral of protocols they approve to this National Committee for review. The existence of one national committee functioning in this way would be helpful to patients in giving them a way of assessing the quality of the protocols in which they may be asked to participate. A rejected proposal could be re submitted after changes.

3.3 Information to be Assessed

A protocol submitted to an REB for gene transfer involving somatic cells in human subjects should include specific information concerning (1) the objectives of the proposed study, (2) the scientific design, (3) the relevant ethical issues, and (4) the qualifications of the researchers and the adequacy of the facilities. Details on the kinds of information needed are set out below. This list is not exhaustive but notes the kinds of issues that should be examined.

3.3.1 Reasons for the Proposed Research

Information regarding the natural history, frequency, and range of expression of the disease should be provided. Available conventional treatment and the advantages and disadvantages of this treatment compared with those of proposed research on gene therapy should be outlined. Information concerning the expected clinical benefits of the proposed research should be presented.

3.3.2 Scientific Design

Detailed information on every aspect of the proposed research must be provided along with relevant data from animal or cellular studies.

The Disease and the DNA to be transferred:

— Which gene is to be transferred? Information about sequence and source.

— What data from animal trials are available on safety and efficiency? Have non-human primate studies been done? If these have not been done, then justification of why this is not possible or appropriate should be given.

— If the gene to be transferred is a non-human genetic sequence, what are the reasons for this choice rather than a human sequence?

— Are any other sequences to be used? Provide information about their source, the reasons for their use and other relevant biological data.

Delivery:

A full description of the preparation, structure and composition of the material to be administered should be provided.

— How will the DNA be transferred to the research subject? If viral vectors are to be used, how is the virus prepared, purified, disabled and tested?

— What is the purity of the DNA to be transferred and how is that assessed?

— What cell line is producing the viral vector?

— Has there been any assessment of "live" viral particles in the treatment of animals?

— How many cells will be used?

Targets and Efficiency:

— What cells are to be used as targets?

— What are the details and experimental basis for claims of efficiency of the means of transferring the DNA?

— What, if any, method of enhanced selection is to be used? What are the risks of this?

Expression:

— What information exists on the likelihood of expression in an appropriate cell line?

— What data are there that this may be sufficient to produce clinical effects? Are animal expression studies available?

— What other information exists that the product of the gene is likely to be expressed sufficiently?

Risks and Safety:

— What steps have been taken to minimize instability, pathogenicity, and how have these been tested?

— What information is there on the likelihood of transfer being confined to the target tissue? Specifically, what is the risk of transfer to cells of the germ line? If it appears that this is likely, then it would be inappropriate to pursue human trials.

— What is the risk that harmful side-effects of treatment will arise later on? How will the subject be monitored for beneficial or harmful effects? What are the clinical end points to be measured? Over what time period? What will be evaluated?

— What mechanism will be used for follow-up of offspring? What measures will be taken to optimize the patient's compliance with follow-up? What measures will be taken to control or reverse the adverse effects if they occur?

— How is the estimate of risks to lab-workers and the general population derived? What precautions are taken to mitigate these risks?

— Do the benefits outweigh the risks to the patient?

— Is the documentation of this adequate to make judgements with regard to safety and efficacy?

— Are the social benefits no less than the social risks?

Other Issues:

— If there are harmful effects, how will this information be communicated to the local and national REB's?

— Will any adjunct treatment be used in addition?

3.3.3 Relevant Ethical Issues

Consent:

— Are details of the information to be given to prospective research subjects, or their proxies (i.e. parent(s) or legal guardian(s)) appropriate?

— Is there full disclosure if a patient's cells or DNA are to be used for any other purpose than to be re-inserted into them?

— Is consent to be sought for what is to be done with their tissue, cells, or DNA?

— How will the investigators conducting the proposed research be identified to the subject or proxy?

— Have the person(s) who will seek consent, the persons or proxies from whom the consent will be sought, and any person(s) who will witness the consent process, been identified?

— Is the consent form acceptable?

— Is it clear whether the consent of the subject will be solicited, or whether a proxy consent will be sought (and if so, from whom)?

— Is there documentation that the subject (or proxy) understands the need for and consents to long term follow-up? Is counselling available to the subject and guardian?

Selection of Candidate Genetic Diseases:

— Does the genetic disorder cause serious disease for which there is no effective alternative treatment?

— What are the chances that the genetically modified cells will benefit the patients by causing an effective treatment of the disease?

Selection of Research Subjects:

— Are the selection criteria to be used fair and equitable?

— Is information regarding recruitment procedures provided?

Privacy and Confidentiality:

— In view of the intense interest of the media in this topic, are sufficient precautions and procedures for preserving privacy and confidentiality clearly specified?

3.3.4 Qualifications of the Researchers and Adequacy of the Research Facilities

— Is sufficient information on the training, experience and institutional affiliations of the investigators submitted to allow evaluation of their qualifications for carrying out research with human subjects in this areas?

— Are the medical personnel involved in the research identified and details on their training and experience given? Only teams with extensive experience in the many clinical and scientific disciplines required should be permitted to undertake research on somatic cell gene transfer in humans.

— Is the hospital or clinic where the research will be undertaken identified?

— Are the facilities which will be available to the research subject (e.g. hospital beds) detailed?

3.4 Composition of a National Review Committee

It is strongly recommended that the MRC should form a committee to review proposals involving gene transfer in humans. It is important to have views from different fields and perspectives participating on the committee. Therefore it should include scientific expertise in the area, representatives from medicine, law, and ethics. A lay individual from a group involved with such genetic diseases (a parent) might also give a useful perspective.

The committee should be empowered to add additional members on an ad hoc basis to provide appropriate expertise in judging a particular proposal.

CONCLUSIONS

The Working Group concludes:

1. The rapid growth of knowledge in human genetics in Canada and in other countries is now leading to proposals to undertake research in somatic cell gene therapy to attempt to treat some inherited disorders which cause devastating and presently untreatable disease and early death.

2. For the foreseeable future, research in humans on gene therapy should be considered only for diseases which meet all the following criteria:

— they are caused by a defect in a single gene

— they cause a liveborn human being to suffer severe debilitation or early death

— they cannot be treated successfully by any other means.

3. For the foreseeable future, there should be no attempts to undertake research in humans which involves deliberate alteration of the patient's germ line, or which involves gene transfer in human embryos.

4. Research with animals and with other models in the area of somatic cell gene therapy for humans is needed and appropriate.

5. Any attempt to treat an inherited disease by somatic cell gene therapy should be regarded as a research protocol, and subject to procedures and considerations as outlined in this document and in the MRC's *Guidelines on Research Involving Human Subjects*.

6. A National Review Committee should be formed to evaluate all proposals in Canada for research on somatic cell gene therapy in humans. A prerequisite for submitting protocols to the National Review Committee is that they should first have been accepted by their local Research Ethics Board.

This is a rapidly evolving area of investigation which has, for the first time, raised the hope of eventual treatment for some devastating human genetic disorders. However, because it is breaking new ground and setting precedents, it is essential that this research be approached with judgment and wisdom. It is the Working Group's belief that following the guidelines outlined in this document will help to ensure this outcome.

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